

WO9616016

Publication Title:

NOVEL (+)-(S)-2-(3-BENZOYLPHENYL)PROPIONIC ACID DERIVATIVES WITH ANALGESIC ACTION AND THE PROCESS FOR THE PREPARATION THEREOF

Abstract:

Abstract of WO 9616016

(A1) Translate this text The present invention relates to novel (+)-(S)-2-(3-benzoylphenyl)propionic acid salts of formula (I), wherein B<+> is choline or the protonated form of lysine, arginine, ornithine, D-glucamine, N-methyl-D-glucamine or imidazole. The process for the preparation comprises reacting a compound of formula (II) with lysine, arginine, ornithine, choline hydroxide, D-glucamine, N-methyl-D-glucamine or imidazole; or reacting a salt of the compound of formula (II) with the suitable organic salt. Said compounds have a high analgesic and antiinflammatory activity.

Courtesy of <http://v3.espacenet.com>



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :

C07C 59/84, A61K 31/19

A1

(11) International Publication Number:

WO 96/16016

(43) International Publication Date:

30 May 1996 (30.05.96)

(21) International Application Number: PCT/EP95/04554

(22) International Filing Date: 20 November 1995 (20.11.95)

(30) Priority Data:

P 9402406

23 November 1994 (23.11.94) ES

(71) Applicant (for all designated States except US): LABORATORIOS MENARINI S.A. [ES/ES]; Alfonso XII, 587, E-08912 Badalona (ES).

(72) Inventors; and

(75) Inventors/Applicants (for US only): MAULEON CASELLAS, David [ES/ES]; Narcis Monturiol, 5, 6^o-4^a, E-08191 Rubí (ES). GARCIA PEREZ, María Luisa [ES/ES]; Alsina i Sensat 8, 1^o-1^a, E-08320 El Masnou (ES). FOS TORRO, María de los Desamparados [ES/ES]; Madrazo, 56, 1^o-2^a, E-08006 Barcelona (ES).

(74) Agents: MINOJA, Fabrizio et al.; Studio Consulenza Brevettuale, Via Rossini, 8, I-20122 Milano (IT).

(81) Designated States: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MX, NO, NZ, PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG).

Published

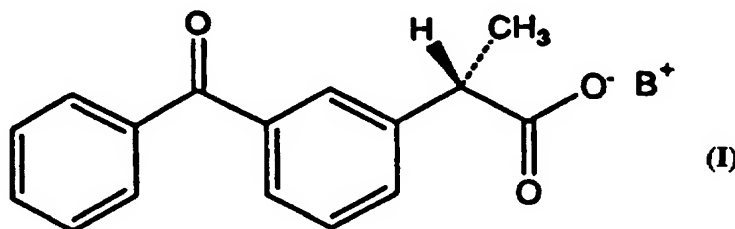
With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NOVEL (+)-(S)-2-(3-BENZOYLPHENYL)PROPIONIC ACID DERIVATIVES WITH ANALGESIC ACTION AND THE PROCESS FOR THE PREPARATION THEREOF

(57) Abstract

The present invention relates to novel (+)-(S)-2-(3-benzoylphenyl)propionic acid salts of formula (I), wherein B⁺ is choline or the protonated form of lysine, arginine, ornithine, D-glucamine, N-methyl-D-glucamine or imidazole. The process for the preparation comprises reacting a compound of formula (II) with lysine, arginine, ornithine, choline hydroxide, D-glucamine, N-methyl-D-glucamine or imidazole; or reacting a salt of the compound of formula (II) with the suitable organic salt. Said compounds have a high analgesic and antiinflammatory activity.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgystan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

NOVEL (+)-(S)-2-(3-BENZOYLPHENYL)PROPIONIC ACID DERIVATIVES WITH ANALGESIC ACTION AND THE PROCESS FOR THE PREPARATION THEREOF

The present invention relates to novel (+)-(S)-2-(3-benzoylphenyl)propionic acid derivatives, namely the salts with basic amino acids, amines or basic heterocycles, the pharmaceutically acceptable solvates thereof, and the pharmaceutical compositions containing them, having anti-inflammatory and analgesic activities. The present invention also relates to a process for the preparation of the novel salts and the therapeutical use thereof.

10 TECHNOLOGICAL BACKGROUND

2-(3-Benzoylphenyl)propionic acid, also named ketoprofen, is a known non-steroidal anti-inflammatory agent exhibiting a potent analgesic and antipyretic action.

15 Though ketoprofen has been marketed as a racemic mixture of its (+)-(S) and (-)-(R) enantiomers, its therapeutical activity has been found to lie mainly in the S enantiomer [Yamaguchi T. et al., *Folia Pharmacol. Japon* 90, 295 (1987)]. Moreover, the (+)-(S) enantiomer
20 of ketoprofen has been claimed to be a faster acting and more potent analgesic than the racemate, when administered at equal doses [Sunshine A. et al., WO 89/04658].

Structurally ketoprofen, similarly to other
25 arylpropionic acids, has a lipophilic aromatic moiety which is responsible for its poor solubility in water and a free carboxylic group which has been related to

its ulcerogenic toxicity. These drawbacks can restrict its use, since its poor solubility makes both the parenteral and oral administrations difficult, and its tendency to cause gastric lesions limits its use in patients prone to gastrointestinal disorders.

According to literature, said drawbacks of arylpropionic acids may substantially be overcome by salifying them with metals, to give salts such as ketoprofen sodium, zinc or aluminium salt [Fujimura H. et al., *Oyo Yakuri*, 13, 709 (1977), Buxadè A. ES 2016503, Montanari R. DE 3505582, respectively]; with basic amino acids such as ibuprofen [Kwan K.Ch. EP 424028] and ketoprofen [Metz G. EP 136470, BE 882889, Bruzzese T. et al., DE 2508895] lysine salts; amine salts such as diclofenac choline salt [Di Schiena M.G. EP 521393]; salts with basic heterocycles such as ketoprofen imidazolium salt [Stradi R. FR 2580641].

(+)-(S)-2-(3-Benzoylphenyl)propionic acid tromethamine salt has also been described [Carganico G. et al., WO 94/11332]; undoubtedly, up to now, no salts of the present invention have been described in literature, therefore said compounds can be considered an alternative to the above cited tromethamine salt.

Nevertheless, in therapy there is a need for compounds with high anti-inflammatory and analgesic activities, free from undesired side-effects. The present invention provides a series of novel compounds showing the cited anti-inflammatory and analgesic actions, together with a very reduced gastrolesivity.

The novel salts have a high solubility in water which allows for them to be administered both

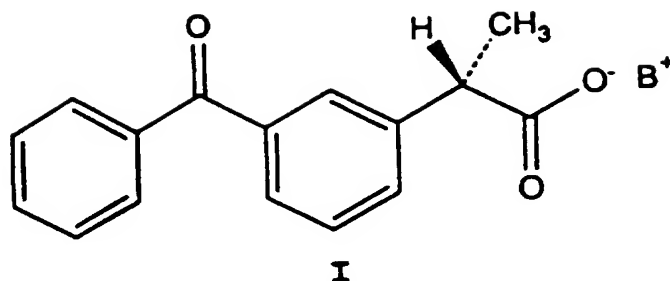
intramuscularly and intravenously, as well as orally in the form of tablets which are easy to dissolve in a very short time. These novel derivatives exhibit a fast, complete adsorption both in animals and humans, showing an action and analgesic response higher than those of the corresponding racemic ketoprofen salts.

Moreover, said characteristics of the compounds of the present invention allow to attain the same analgesic therapeutical effectiveness using doses lower than those necessary for racemic ketoprofen, either free or salified. Further, the physico-chemical and pharmacokinetic properties of the compounds of the present invention give them a therapeutical advantage compared with the use of the (+)-(S) enantiomer of ketoprofen in the free acid form, claimed in the above cited patent [Sunshine A. et al., WO 89/04658], also showing an additional advantage, since they can be administered to patients prone to gastrointestinal disorders when treated with ketoprofen free acid and can be considered an alternative to the metal salts when the metal retention is contra-indicated, for example in case of patients suffering from cardiac disorders or hypertension.

DISCLOSURE OF THE INVENTION

The present invention provides novel salts of general formula (I),

4



wherein:

B^+ is choline or the protonated form of lysine,
10 arginine, ornithine, D-glucamine, N-methyl-D-glucamine
or imidazole.

The present invention also provides a process for
the preparation of the novel (+)-(S)-2-(3-benzoyl-
phenyl)propionic acid salts, as well as the
15 therapeutical use thereof.

Object of the present invention are also the
solvates of the compounds of formula (I).

The present invention also includes all the
possible stereoisomers of the compounds of formula (I)
20 as well the mixtures thereof.

Preferred compounds of the present invention are
those wherein B^+ is choline or the protonated form of
L-lysine, DL-lysine, L-arginine, DL-arginine,
N-methyl-D-glucamine or imidazole.

25 Particularly preferred compounds of the present
invention are the following ones:

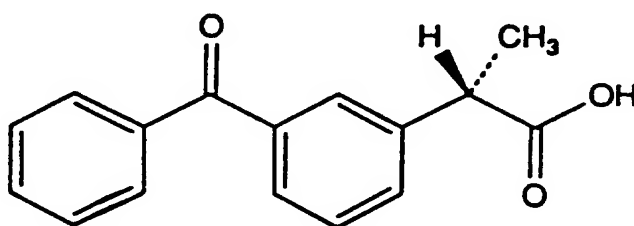
(+)-(S)-2-(3-benzoylphenyl)propionic acid L-lysine salt;
(+)-(S)-2-(3-benzoylphenyl)propionic acid DL-lysine
salt;

30 (+)-(S)-2-(3-benzoylphenyl)propionic acid choline salt;
(+)-(S)-2-(3-benzoylphenyl)propionic acid N-methyl-D-

glucamine salt;

(+)-(S)-2-(3-benzoylphenyl)propionic acid imidazole salt.

According to the present invention, the compounds
of formula (I) are obtained by reacting (+)-
(S)-2-(3-benzoylphenyl)propionic acid (II)



II

with lysine, arginine, ornithine, choline hydroxide, D-glucamine, N-methyl-D-glucamine or imidazole; or by
reacting a (+)-(S)-2-(3-benzoylphenyl)propionic acid
(II) salt, prepared *in situ* (preferably the sodium salt)
with the suitable organic salt, such as lysine, arginine
or ornithine hydrochloride or choline chloride. The
reaction is carried out preferably in equimolar amounts,
in a solvent or in a mixture of polar solvents such as
water, ethanol, isopropanol, methanol, tetrahydrofuran
or acetone. Preferably, a mixture of water with methanol
or ethanol is used and, when employing the sodium salt
of the compound of formula (II), ethanol or isopropanol
with a low water content are preferably used to promote
the precipitation of sodium chloride formed during the
reaction. The reaction temperature can vary between 0°C
and the solvent reflux, for a time between 1 and 24
hours.

The starting (+)-(S)-2-(3-benzoylphenyl)propionic
acid (II) can be prepared following the procedures

described in literature, for example by enantioselective synthesis [Fadel A., *Synlett.* 1, 48 (1992)], or by resolution of racemic ketoprofen through crystallization with chiral amines or enzymatic methods [Nohira H. et al., EP 423467, Sih C.L. et al., EP 227078, Carganico G. et al., WO 93/25703, WO 93/25704, Evans C. et al., WO 93/04189, WO 93/04190, Warneck J. et al., WO 94/20633].

The compounds of the present invention have anti-inflammatory and analgesic characteristics and therefore they can be used in human therapy.

For the therapeutical use, the compounds of the present invention are formulated in suitable pharmaceutical forms, according to conventional techniques and excipients, such as those described in Remington's Pharmaceutical Handbook, Mack Pub. Co., N.Y., USA. Examples of such formulations include capsules, tablets, granulates, solutions, syrups and the like, containing 1 to 1000 mg per unitary dose.

The following examples illustrate the preparation and the results of the pharmacological activity tests of the compounds of the present invention, without limiting it.

EXAMPLE 1

Preparation of (+)-(S)-2-(3-benzoylphenyl)propionic acid L-lysine salt

To a solution of (+)-(S)-2-(3-benzoylphenyl)propionic acid (5.0 g, 19.7 mmol) in ethanol (8 ml), a solution of L-(+)-(S)-lysine (2.85 g, 19.5 mmol) in water (10 ml) was added. The mixture was stirred at room temperature for 1 hour, thereafter was evaporated to dryness to obtain a semi-solid residue which was

redissolved in ethanol and evaporated to dryness to obtain a solid, which was digested in ethyl ether (3x50ml), filtered and dried under vacuum. 6.59 g (84%) of the title compound were obtained as a white solid with melting point 141.8-142.6°C.

5 $[\alpha]_D^{25} = +3.07^\circ$ (c = 1.24, water).

IR (KBr): 2960, 2930, 1650, 1640, 1600, 1570, 1490, 1400, 1360, 1290, 720, 650 cm^{-1} .

1H N.M.R. (300 MHz, CD_3OD) δ ppm: 1.45 (d, 3H); 1.48 (m, 2H); 1.64 (m, 2H); 1.84 (m, 2H); 2.88 (t, 2H); 3.55 (t, 1H); 3.66 (q, 1H); 7.41-7.80 (m, 9H).

Elemental analysis: calculated for $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}_5$: C, 65.98%; H, 7.05%; N, 6.99%. Found: C, 65.79%; H, 7.14%; N, 6.99%.

15 EXAMPLE 2

Preparation of (+)-(S)-2-(3-benzoylphenyl)propionic acid DL-lysine salt

(+)-(S)-2-(3-Benzoylphenyl)propionic acid was reacted with DL-lysine analogously to what described in Example 1. A water-soluble white solid was obtained.

20 EXAMPLE 3

Preparation of (+)-(S)-2-(3-benzoylphenyl)propionic acid choline salt

To a choline hydroxide aqueous solution (0.95 g, 7.87 mmol), (+)-(S)-2-(3-benzoylphenyl)propionic acid (2.0 g, 7.87 mmol) was added. The mixture was heated to 60°C for 10 hours, thereafter was evaporated to dryness, to obtain a semi-solid residue which was redissolved in ethanol and evaporated to dryness. The resulting solid was filtered and washed with ethyl ether. 2.52 g (89%) of a white solid were obtained.

8

Elemental analysis: calculated for $C_{21}H_{27}NO$: C, 70.56%; H, 7.61%; N, 3.92%. Found: C, 70.12%; H, 7.31%; N, 3.62%.

EXAMPLE 4

5 Preparation of (+)-(S)-2-(3-benzoylphenyl)propionic acid
N-methyl-D-glucamine salt

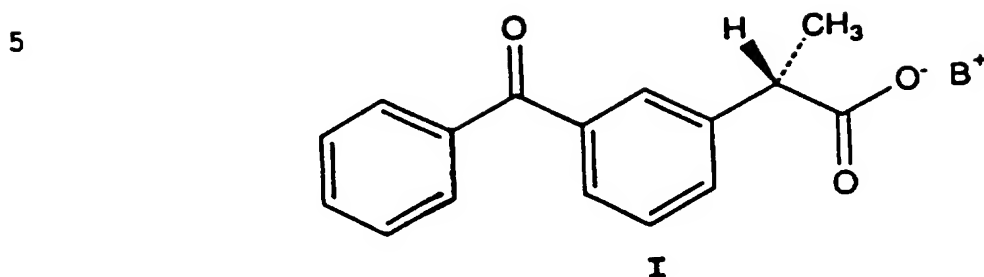
To a solution of (+)-(S)-2-(3-benzoylphenyl)propionic acid (2.5 g, 9.8 mmol) in ethanol (10 ml), a solution of N-methyl-D-glucamine (1.01 g, 9.8 mmol) in water (12 ml) was added. The mixture was stirred at 30°C for 1 hour, thereafter was evaporated to dryness. The resulting residue was redissolved in ethanol and evaporated to dryness. The obtained solid was digested with cold ethyl ether, filtered and dried under vacuum. 3.97 g (90%) of a white solid were obtained.

10

15

CLAIMS

1. A compound of formula (I),



10

wherein:

B⁺ is choline or the protonated form of lysine, arginine, ornithine, D-glucamine, N-methyl-D-glucamine or imidazole; all the possible stereoisomers of compound (I) and the mixtures thereof, as well as the pharmaceutically acceptable solvates of compound (I).

15

2. A compound according to claim 1, wherein B⁺ is choline or the protonated form of L-lysine, DL-lysine, L-arginine, DL-arginine, N-methyl-D-glucamine or imidazole.

20

3. A compound according to the above claims, selected from:

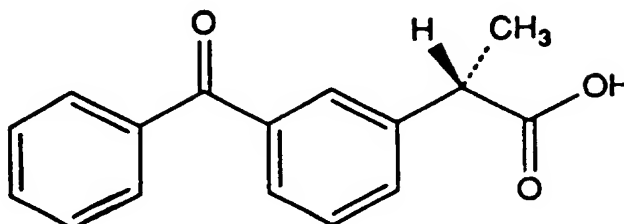
(+)-(S)-2-(3-benzoylphenyl)propionic acid L-lysine salt;
(+)-(S)-2-(3-benzoylphenyl)propionic acid DL-lysine salt;
25 (+)-(S)-2-(3-benzoylphenyl)propionic acid choline salt;
(+)-(S)-2-(3-benzoylphenyl)propionic acid N-methyl-D-glucamine salt;
(+)-(S)-2-(3-benzoylphenyl)propionic acid imidazole salt.
30

4. A process for the preparation of the compounds of

10

general formula (I) of claim 1, which process comprises reacting a compound of formula (II):

5



II

10 with lysine, arginine, ornithine, choline hydroxide, D-glucamine, N-methyl-D-glucamine or imidazole; or reacting a salt of the compound of formula (II), prepared in situ, with the suitable organic salt selected from lysine, arginine or ornithine
15 hydrochloride or choline chloride, the reaction being carried out in a solvent or in a mixture of polar solvents, selected from water, ethanol, isopropanol, methanol, tetrahydrofuran or acetone.

5. A process according to claim 4, wherein the salt of
20 compound (II) prepared in situ is the sodium salt.

6. A process according to claim 4, wherein the solvent is a mixture of water and methanol or ethanol, and, when using the sodium salt of the compound of formula (II), low water content ethanol or isopropanol
25 are used.

7. The use of a compound according to any one of claims 1 to 3 for the preparation of a medicament for producing a rapid, high analgesic response in humans.

8. The use of a compound according to any one of
30 claims 1 to 3 for the preparation of a medicament for the treatment of pain and inflammation in humans.

9. Pharmaceutical compositions containing a therapeutically effective amount of a compound according to claims 1 to 3, together with a pharmaceutically acceptable excipient.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 95/04554

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C59/84 A61K31/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,94 20449 (DOMPE'FARMACEUTICI SPA) 15 September 1994 ENTIRE DOCUMENT.	1-9
A	US,A,5 179 097 (ANGRES) 12 January 1993 see claims 1,3,8	1



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

14 March 1996

Date of mailing of the international search report

25.03.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

Klag, M

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 95/04554

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9420449	15-09-94	AU-B- 6290594	26-09-94
US-A-5179097	12-01-93	NONE	